General

Guideline Title

Lower limb peripheral arterial disease: diagnosis and management.

Bibliographic Source(s)

National Clinical Guideline Centre. Lower limb peripheral arterial disease: diagnosis and management. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 28 p. (Clinical guideline; no. 147).

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Information Requirements

Offer all people with peripheral arterial disease oral and written information about their condition. Discuss it with them so they can share decision-making, and understand the course of the disease and what they can do to help prevent disease progression. Information should include:

- The causes of their symptoms and the severity of their disease
- The risks of limb loss and/or cardiovascular events associated with peripheral arterial disease
- The key modifiable risk factors, such as smoking, control of diabetes, hyperlipidaemia, diet, body weight, and exercise (see also the related recommendation in the section "Secondary Prevention of Cardiovascular Disease in People with Peripheral Arterial Disease," below)
- How to manage pain
- All relevant treatment options, including the risks and benefits of each
- How they can access support for dealing with depression and anxiety

Ensure that information, tailored to the individual needs of the person, is available at diagnosis and subsequently as required, to allow people to make decisions throughout the course of their treatment.

NICE has produced guidance on the components of good patient experience in adult National Health Service (NHS) services. Follow the recommendations in Patient Experience in Adult NHS Services (NICE clinical guideline 138).

Secondary Prevention of Cardiovascular Disease in People with Peripheral Arterial Disease

Offer all people with peripheral arterial disease information, advice, support, and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance (see section 6 of the original guideline document) on:

- Smoking cessation
- Diet, weight management, and exercise
- Lipid modification and statin therapy
- The prevention, diagnosis, and management of diabetes
- The prevention, diagnosis, and management of high blood pressure
- Antiplatelet therapy

Diagnosis

Assess people for the presence of peripheral arterial disease if they:

- Have symptoms suggestive of peripheral arterial disease or
- Have diabetes, non-healing wounds on the legs or feet, or unexplained leg pain or
- Are being considered for interventions to the leg or foot or
- Need to use compression hosiery

Assess people with suspected peripheral arterial disease by:

- Asking about the presence and severity of possible symptoms of intermittent claudication and critical limb ischaemia
- Examining the legs and feet for evidence of critical limb ischaemia, for example ulceration
- Examining the femoral, popliteal, and foot pulses
- Measuring the ankle brachial pressure index (see next recommendation)

Measure the ankle brachial pressure index in the following way:

- The person should be resting and supine if possible.
- Record systolic blood pressure with an appropriately sized cuff in both arms and in the posterior tibial, dorsalis pedis and, where possible, peroneal arteries.
- Take measurements manually using a Doppler probe of suitable frequency in preference to an automated system.
- Document the nature of the Doppler ultrasound signals in the foot arteries.
- Calculate the index in each leg by dividing the highest ankle pressure by the highest arm pressure.

Imaging for Revascularisation

Offer duplex ultrasound as first-line imaging to all people with peripheral arterial disease for whom revascularisation is being considered.

Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging (after duplex ultrasound) before considering revascularisation.

Offer computed tomography angiography to people with peripheral arterial disease who need further imaging (after duplex ultrasound) if contrast-enhanced magnetic resonance angiography is contraindicated or not tolerated.

Management of Intermittent Claudication

Supervised Exercise Programme

Offer a supervised exercise programme to all people with intermittent claudication.

Consider providing a supervised exercise programme for people with intermittent claudication which involves:

- 2 hours of supervised exercise a week for a 3-month period
- Encouraging people to exercise to the point of maximal pain

Angioplasty and Stenting

Offer angioplasty for treating people with intermittent claudication only when:

- Advice on the benefits of modifying risk factors has been reinforced (see the related recommendation in the section "Secondary Prevention of Cardiovascular Disease in People with Peripheral Arterial Disease," above) and
- A supervised exercise programme has not led to a satisfactory improvement in symptoms and
- Imaging has confirmed that angioplasty is suitable for the person

Do not offer primary stent placement for treating people with intermittent claudication caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.

Consider primary stent placement for treating people with intermittent claudication caused by complete aorto-iliac occlusion (rather than stenosis).

Use bare metal stents when stenting is used for treating people with intermittent claudication.

Bypass Surgery and Graft Types

Offer bypass surgery for treating people with severe lifestyle-limiting intermittent claudication only when:

- Angioplasty has been unsuccessful or is unsuitable and
- Imaging has confirmed that bypass surgery is appropriate for the person

Use an autologous vein whenever possible for people with intermittent claudication having infra-inguinal bypass surgery.

Naftidrofuryl Oxalate

Consider naftidrofuryl oxalate for treating people with intermittent claudication, starting with the least costly preparation, only when:

- Supervised exercise has not led to satisfactory improvement and
- The person prefers not to be referred for consideration of angioplasty or bypass surgery

Review progress after 3–6 months and discontinue naftidrofuryl oxalate if there has been no symptomatic benefit.

Management of Critical Limb Ischaemia

Ensure that all people with critical limb ischaemia are assessed by a vascular multidisciplinary team before treatment decisions are made.

Revascularisation

Offer angioplasty or bypass surgery for treating people with critical limb ischaemia who require revascularisation, taking into account factors including:

- Comorbidities
- Pattern of disease
- Availability of a vein

- Patient preference

Do not offer primary stent placement for treating people with critical limb ischaemia caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.

Consider primary stent placement for treating people with critical limb ischaemia caused by complete aorto-iliac occlusion (rather than stenosis).

Use bare metal stents when stenting is used for treating people with critical limb ischaemia.

Use an autologous vein whenever possible for people with critical limb ischaemia having infra-inguinal bypass surgery.

Management of Critical Limb Ischaemic Pain

Offer paracetamol, and either weak or strong opioids depending on the severity of pain, to people with critical limb ischaemic pain.

Offer drugs such as laxatives and anti-emetics to manage the adverse effects of strong opioids, in line with the person's needs and preferences.

Refer people with critical limb ischaemic pain to a specialist pain management service if any of the following apply:

- Their pain is not adequately controlled and revascularisation is inappropriate or impossible.
- Ongoing high doses of opioids are required for pain control.
- Pain persists after revascularisation or amputation.

Do not offer chemical sympathectomy to people with critical limb ischaemic pain, except in the context of a clinical trial.

Major Amputation

Do not offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team.

Clinical Algorithm(s)

The recommendations from this guideline have been incorporated into a NICE pathway .

Scope

Disease/Condition(s)

Lower limb peripheral arterial disease

Other Disease/Condition(s) Addressed

Pain

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Nursing

Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Hospitals

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To provide guidelines on the diagnosis and management of lower limb peripheral arterial disease (PAD)

Note: These guidelines do not cover:

> Screening of asymptomatic PAD
> Methods of amputation and rehabilitation
> Management of diabetic foot problems
> Use of topical treatments and dressings

Target Population

Adults aged 18 and older, including:

- People who present with symptoms of lower limb peripheral arterial disease (PAD), including intermittent claudication, ischaemic rest pain, and/or tissue loss
- People without symptoms of peripheral arterial disease (for example, those with venous ulceration) who have abnormal ankle/brachial pressure index (ABPI)
- Subgroups based on ethnicity, socioeconomic factors, age, or comorbidities (including people with diabetes), for which differences in management and outcome are identified

Note: These guidelines are not intended for use in the following patients:

> Children and young people aged 17 and younger

Adults who have acute ischaemia of the lower limb

Interventions and Practices Considered

Assessment/Diagnosis

1. Assess people for the presence of peripheral arterial disease
    - Assessment of signs and symptoms
    - Presence of diabetes, non-healing wounds on the legs or feet or unexplained leg pain
2. Assess people with suspected peripheral arterial disease
    - Physical examination for evidence of critical limb ischaemia
    - Examination of femoral, popliteal, and foot pulses
    - Measurement of ankle brachial pressure index
3. Imaging
    - Duplex ultrasound
    - Contrast-enhanced magnetic resonance angiography
    - Computed tomography angiography
4. Assessment of patients with critical limb ischaemia by a vascular multidisciplinary team

Management/Treatment

1. Provision of patients with oral and written information
2. Secondary prevention of cardiovascular disease
    - Smoking cessation
    - Diet, weight management, and exercise
    - Lipid modification and statin therapy
    - Prevention, diagnosis, and management of diabetes
    - Prevention, diagnosis, and management of high blood pressure
    - Antiplatelet therapy
3. Management of intermittent claudication
    - Supervised exercise programme
    - Angioplasty
    - Primary stent placement
    - Bypass surgery (autologous vein if possible)
    - Naftidrofuryl oxalate
4. Management of critical limb ischaemia
    - Angioplasty
    - Primary stent placement
    - Bypass surgery (autologous vein if possible)
5. Management of critical limb ischaemic pain
    - Paracetamol
    - Opioids (plus laxatives and anti-emetics as needed)
6. Major amputation

Major Outcomes Considered

- Mortality
- Health-related quality of life
- Walking distance
- Limb salvage rates
- Graft and vessel patency (primary and secondary)
- Re-intervention rates
- Re-admission rates
- Adverse events

- Pain intensity scale
- Cardiovascular morbidity
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Clinical Literature Search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per the Guidelines Manual 2009 (see the "Availability of Companion Documents" field). Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl, and The Cochrane Library. In addition, PsychInfo database was used for the patient information review question. All searches were updated on the 9th January 2012. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the guideline development group (GDG) for known studies. The questions, the study types applied, the databases searched, and the years covered can be found in Appendix D of the full version of the original guideline document.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearinghouse (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (www.consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

Call for Evidence

The GDG decided to initiate a 'call for evidence' for randomised controlled trials comparing the effectiveness of drug eluting stents to bare metal stents for the treatment of peripheral arterial disease as they believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence.

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to people with peripheral arterial disease in the National Health Service economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2010, to

ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D of the full version of the original guideline document (see the "Availability of Companion Documents" field). All searches were updated on the 9th January 2012. No papers published after this date were considered.

Evidence of Effectiveness

The research fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C of the full version of the original guideline document [see the "Availability of Companion Documents" field]).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual 2009 (see the "Availability of Companion Documents" field)
- Extracted key information about the study's methods and results into evidence tables (clinical evidence tables are included in Appendix H [see the "Availability of Companion Documents" field])
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
    - Randomised studies: meta-analysed, where appropriate and reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for clinical studies)
    - Observational studies: data presented as a range of values in GRADE profiles
    - Diagnostic studies: data presented as a range of values in adapted GRADE profiles
    - Qualitative studies: each study summarised in adapted GRADE profiles

Inclusion/Exclusion

The inclusion/exclusion of studies was based on the review protocols (see Appendix C of the full version of the original guideline document [see the "Availability of Companion Documents" field]). The GDG were consulted about any uncertainty regarding inclusion/exclusion of selected studies.

Type of Studies

For most intervention evidence reviews in this guideline, randomised controlled trials (RCTs) were included. Where the GDG believed RCT data would not be appropriate this is detailed in the protocols in Appendix C (see the "Availability of Companion Documents" field). RCTs were included as they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects.

For diagnostic evidence reviews, diagnostic randomised controlled trials, diagnostic cohorts and case controls studies were included in this guideline.

Evidence of Cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought.

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify relevant studies
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual
- Extracted key information about the study's methods and results into evidence tables (included in Appendix I of the full guideline document)
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups in the full guideline document)

Inclusion/Exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-Organisation for Economic Cooperation and Development [OECD] country, except for American studies, which were considered 'partially applicable').

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section and included in the list of excluded studies in Appendix F of the full guideline document (see the "Availability of Companion Documents" field).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist in The Guidelines Manual (see the "Availability of Companion Documents" field).

When no relevant economic analysis was identified in the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

Number of Source Documents

See Appendix G of the full version of the original guideline document for the number of source documents by review question.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation

Level	Description
High	Further research is very unlikely to change the confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: mortality, amputation free survival, cardiovascular events, adverse events, re-intervention rates, and withdrawal rates. The continuous outcomes: quality of life, walking distance, exercise level at follow up, change in ankle brachial pressure index (ABPI) pain measures, duration of pain control, and patient satisfaction were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio.

Three network meta-analyses were considered for the guideline. The three proposed networks were for the outcome of walking distance in the intermittent claudication (IC) population, mortality in the critical limb ischaemia (CLI) population and amputation free survival in the CLI population. None of the network meta-analyses were methodologically possible to conduct due to lack of evidence to build complete networks for the outcomes proposed.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at probability (p) <0.1 or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, a sensitivity analysis was carried out based on the quality of studies if there were differences, with particular attention paid to allocation concealment, blinding, and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data, or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For continuous outcomes, the means and standard deviations were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. When the only evidence was based on studies summarised results by only presenting means this information was included in the GRADE tables without calculating the relative and absolute effect.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Data Synthesis for Diagnostic Test Accuracy Review

Evidence for diagnostic data was evaluated by study, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklists.

For diagnostic test accuracy studies, the following data were extracted, either directly from the study report or calculated from other study data: components of the "2x2 table" (true positives, false positives, false negatives, and true negatives) and test accuracy parameters: sensitivity, specificity, positive/negative predictive values, and positive/negative likelihood ratios (there are other outcomes that can be included such as area under curve [AUC] for receiver operator characteristics [ROC] curves) reproducibility, applicability, and inter- and intra-operative reliability). In cases where the outcomes were not reported, 2x2 tables were constructed from raw data to allow calculation of accuracy measures.

Forest plots of sensitivity and specificity with their 95% confidence intervals were presented side-by-side for individual studies using Cochrane Review Manager (RevMan5) software (for RevMan see Appendix J of the full version of the original guideline document).

When data from five or more studies were available, a diagnostic meta-analysis was carried out. To show the differences between study results, pairs of sensitivity and specificity were plotted for each study on one ROC curve in Microsoft EXCEL software (for Excel plots please see Appendix J). A ROC plot shows true positive rate (i.e., sensitivity) as a function of false positive rate (i.e., 1 – specificity). Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach (in WinBUGS® software - for the program code see Appendix J of the full version of the original guideline document). This model also assesses the variability by incorporating the precision by which sensitivity and specificity have been measured in each study. A confidence ellipse is shown in the graph that indicates the confidence region around the summary sensitivity/specificity point. A summary ROC curve is also presented. From the WinBUGS® output the summary estimate of sensitivity and specificity (plus their 95% confidence intervals) as well as between study variation measured as logit sensitivity and specificity as well as correlations between the two measures of variation are reported. The summary diagnostic odds ratio with its 95% confidence interval is also reported.

Appraising the Quality of Evidence by Outcomes

The evidence for outcomes from the included RCTs and observational studies were evaluated and presented using an adaptation of the 'Grading of

Recommendations Assessment, Development, and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as one table in the full version of the original guideline document (called clinical evidence profiles). This includes the details of the quality assessment pooled outcome data, and where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment.

Each outcome was examined separately for the quality elements listed and defined in Table 4 of the full version of the original guideline document and each graded using the quality levels listed in Table 5 of the full version of the original guideline document and the table shown in the "Rating Scheme for the Strength of the Evidence" field. The main criteria considered in the rating of these elements are discussed in section 3.3.6 "Grading of Evidence" in the full version of the original guideline document. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The GRADE toolbox is currently designed only for RCTs and observational studies but however, for the purposes of this guideline, the quality assessment elements and outcome presentation was adapted for diagnostic accuracy and qualitative studies.

After results were pooled, the overall quality of evidence for each outcome was considered. See section 3.3.6 in the full version of the original guideline document and the "Rating Scheme for the Strength of the Evidence" field for additional detail.

Grading the Quality of Clinical Evidence

After results were pooled, the overall quality of evidence for each outcome was considered (see the "Rating Scheme for the Strength of the Evidence" field). The following procedure was adopted when using Grading of Recommendations Assessment, Development and Evaluation (GRADE):

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed in the full version of the original guideline. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have "serious" or "very serious" risk of bias was rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

Evidence was also appraised for study limitations, inconsistency, indirectness, and imprecision. See sections 3.3.7-3.3.10 in the full version of the original guideline document for detail.

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates (see Table 10 in the full version of the original guideline document). The economic evidence profile includes an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for each assessment. These assessments were made by the health economist using the economic evaluation checklist from the Guidelines Manual 2009. It also shows incremental costs, incremental outcomes (for example, quality-adjusted life years [QALYs]), and the incremental cost-effectiveness ratio, as well as information about the assessment of uncertainty in the analysis.

Several of the pair wise clinical comparisons conducted in the IC population concerned the same decision question. Due to the nature of the question and the difficulty of considering multiple-comparator evaluations in a pair wise context, the clinical and economic evidence for these questions were presented in separate sections in the full version of the original guideline document.

All costs converted into 2009/10 pounds sterling using the appropriate purchasing power parity.

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in priority selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the

review questions and consideration of the available health economic evidence.

The GDG identified the treatment of IC using exercise and endovascular interventions as the highest priority areas for original economic modelling. Specifically, these areas include the cost effectiveness of supervised compared to unsupervised exercise, and exercise compared to angioplasty for the treatment of IC.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible
- When published data was not available GDG expert opinion was used to populate the model
- Model inputs and assumptions were reported fully and transparently
- The results were subject to sensitivity analysis and limitations were discussed
- The model was peer-reviewed by another health economist at the NCGC

Additional data for the analysis was identified as required through additional literature searches undertaken by the health economist and in discussion with the GDG. Model structure, inputs, and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

Full methods for the original health economic analyses undertaken for this guideline are described in Appendices K and L of the full version of the original guideline document.

Cost-Effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'recommendations and link to evidence' section of the relevant chapter of the full version of the original guideline document with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.

In the Absence of Cost-Effectiveness Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between comparators and relevant United Kingdom National Health Service unit costs alongside the results of the clinical review of effectiveness evidence.

Health-Related Quality of Life

Early in the guideline development process, the GDG decided that they wished to inform the economic analyses with health related quality of life obtained directly from the included clinical studies. Changes in disease specific functional disability would be captured by including walking distance as an outcome. The NICE reference case specifies that the EQ-5D is the preferred method of QALY measurement. Therefore, only EQ-5D values or health state descriptions which could be mapped to EQ-5D were included as measures of health related quality of life. Disease specific questionnaires and other generic health profiles were not included as outcomes in the review.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009 (see the "Availability of Companion Documents" field).

Who Developed This Guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline.

The GDG was convened by the NCGC in accordance with guidance from the NICE. The group met every 6-8 weeks during the development of the guideline. Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists, and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analyses and cost-effectiveness analyses where appropriate, and drafted the guideline in collaboration with the GDG.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient/population, intervention, comparison, and outcome) for intervention reviews, and with a framework of population, index tests, reference standard, and target condition for reviews of diagnostic test accuracy (see Table 3 in the full version of the original guideline document). This was to guide the literature searching process and to facilitate the development of recommendations by the GDG. They were drafted by the NCGC technical team and refined and validated by the GDG. The review questions were based on the key clinical areas identified in the scope (Appendix A of the full version of the original guideline document). The review question protocols can be found in Appendix C of the full version of the original guideline document. The review questions and outcome measures examined are presented in Table 3 in the full version of the original guideline document.

Developing Recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I of the full version of the original guideline document.
- Summary of clinical and economic evidence and quality (as presented in chapters 5-12 in the full version of the original guideline document)
- Forest plots, diagnostic meta-analysis, and summary receiver operating characteristic (ROC) curves (see Appendix J of the full version of the original guideline document)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (see Appendix K and L of the full version of the original guideline document).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms, and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences, and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the recommendations and link to evidence section following the clinical and economic evidence reviews in the full version of the original guideline document.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

See the chapters 5-12 in the full version of the original guideline document for discussion of cost-effectiveness by review question.

Cost-Effectiveness Analysis: Supervised Exercise Compared to Unsupervised Exercise for the Treatment of People with Intermittent Claudication

Conclusion = Evidence Statement

The results of the analysis suggest that compared to unsupervised exercise, supervised exercise programmes represent a cost-effective treatment for people with intermittent claudication (IC).

For complete information on this cost-effectiveness analysis, see Appendix K of the full version of the original guideline document (see the "Availability of Companion Documents" field).

Cost-Effectiveness Analysis: Exercise Compared to Angioplasty for the Treatment of Intermittent Claudication

Conclusion = Evidence Statement

According to the model, there is a high degree of uncertainty regarding the most cost-effective sequence of interventions for the treatment of intermittent claudication. The results of the model suggest that supervised exercise followed by angioplasty with selective stent placement has the highest probability of being cost effective in both the aorto-iliac and femoro-popliteal artery.

For complete information on this cost-effectiveness analysis, see Appendix L of the full version of the original guideline document (see the "Availability of Companion Documents" field).

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was validated through two consultations.

1. The first draft of the guideline (the full guideline, National Institute for Health and Clinical Excellence [NICE] guideline, and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG)
2. The final consultation draft of the full guideline, the NICE guideline and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

Validation Process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Clinical Excellence (NICE) website when the pre-publication check of the full guideline occurs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of lower limb peripheral arterial disease

Potential Harms

- Healthcare professionals must be aware of the impact of information on patients. This may have a negative impact or may be misunderstood.
- Ankle brachial pressure index (ABPI) is a non-invasive test and there are no recognised dangers of correct use of equipment. It is important that healthcare professionals are appropriately trained as failure to correctly measure ABPI may result in a misdiagnosis, thereby delaying referral or treatment.
- The guideline development group (GDG) noted that all imaging techniques are relatively safe. The avoidance of intravascular contrast media (not required for duplex ultrasound scanning [DUS]) and of exposure to ionising radiation (not required for DUS or for contrast-enhanced magnetic resonance angiography [CE-MRA]) are important considerations. Allergic reactions to contrast medium are rare, but the potential nephrotoxic effects of iodinated contrast media are of concern. Whilst digital subtraction angiography (DSA) is considered the gold standard, it is much less commonly used in routine practice. It involves both administration of a contrast medium and ionising radiation. In addition, discomfort is experienced by some patients. DUS was not perceived as having any major risks. DUS may be technically more difficult in large or obese patients and/or in the presence of calcification (particularly in diabetic patients) or where there are ulcers and bandaging near the sites of the vessels. Stenosis and occlusion are important with regard to sensitivity of DUS for below knee lesions.
- Based on their collective clinical experience, the GDG agreed that the risks associated with a supervised exercise programme are minimal. Both exercise interventions (supervised and unsupervised) require a time commitment from the patient. Supervised exercise may also be associated with transportation costs. These considerations should be discussed with each patient on an individual basis.
- The GDG were of the opinion that, because it may be more convenient to prescribe a drug than to refer for further assessment for an invasive intervention, there is a risk that naftidrofuryl may sometimes be used when other treatment modalities (e.g., revascularisation) are likely to be superior in terms of outcomes.
- Comparison of adverse effects in studies comparing treatment options was hard to synthesize, and indeed the three interventions all have very different potential risks. Exercise therapy is non-invasive, but carries the risk of exacerbating problems such as those caused by chronic musculoskeletal disease. Angioplasty can produce local haematomas and these were reported in the studies evaluated. Bypass surgery is associated with significant risks including those of an anaesthetic, haematoma, and wound infection, and these should be discussed fully with the patient. The complication rates in the studies directly comparing angioplasty to surgery were not significantly different, and nor were re-intervention rates at the time points reported.
- There is a problem with compliance to supervised exercise programmes, which may limit their usefulness, partly related to the willingness and ability of people to attend them. The studies reported that withdrawal rates were related to distance from home and lack of transport.
- The GDG were concerned that stents may give the operator the impression that a procedure has been technically successful at the time the procedure is performed, but noted that no consistent later benefit was demonstrated in comparison with angioplasty.
- The GDG considered that the routine use of stents as opposed to selective use in conjunction with angioplasty carried the disadvantages of additional cost, increased procedure time, and potential risks of additional instrumentation.
- Endovascular procedures carry a potential risk of causing embolisation of material from the diseased artery which can cause blockage of smaller arteries further down the leg. This is thought to be a greater risk with complete occlusion of the aorto-iliac arteries than with stenosis or occlusion in smaller vessels. There is also a risk of restenosis following endovascular treatment and having foreign material such as a stent in the artery may increase this risk, particularly in smaller vessels.
- The GDG considered that it is generally accepted that stenting is advantageous in terms of embolisation rates although the evidence reviewed in these studies did not reflect this.
- The GDG noted that the formal evidence suggested benefit from autologous vein grafts in terms of the need for re-intervention but did not show any noteworthy difference in complication rates. There were slightly more peri-operative complications with autologous grafts but the difference was not statistically significant.
- Adverse events were more frequently observed with bypass surgery than with angioplasty, although this difference was significant only for minor events. There was debate around the technical failure rate with angioplasty. Having bypass surgery after angioplasty resulted in poorer outcomes than going straight to bypass in the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) study, which may indicate that angioplasty had changed the bypass opportunity. However, it is also possible that this group of people, who required two procedures were those with a poorer natural prognosis and that they would not have had good results with either procedure. This is difficult to tease out of the study data and the GDG were not unanimous in their view of the implied risk of attempting angioplasty first in people suitable for bypass.
- According to the results of the clinical review, there was no significant difference in mortality, adverse events, and amputation between bare metal and drug eluting stents. The GDG did not feel there was any difference between the two types of stent in terms of technical difficulty in

placement. The method of placement of the two forms of stents is identical, and therefore the main potential adverse effects are also the same.

- The GDG considered the side effects associated with each type of analgesia (such as constipation, nausea, and drowsiness). The group agreed that a tiered approach to pain management would minimise adverse events associated with stronger preparations while ensuring that adequate pain relief was provided. The GDG noted that prolonged use of pain medication is often associated with side-effects, and that tolerance and dependence to pain relief need to be considered. Patients should therefore be reviewed on a regular basis. Particular note was taken of the potential risks of prolonged strong opioid use, and the GDG felt that this situation should be one in which advice from, and monitoring by, a pain specialist should be sought.
- Major amputation is associated with high risk of mortality and morbidity and is therefore considered as a last measure for the treatment of pain associated with critical limb ischaemia. Specifically, the post-operative mortality rate for amputation is the highest of all vascular procedures. People can further develop pressure sores, phantom limb pain, and stump problems. In addition, further amputation is common. There is also the loss of independence and emotional difficulties.
- Observational studies (not reviewed), and clinical experience of the GDG suggest that prosthetic material is associated with more infection and poorer limb salvage rates. As a result, there has been a change in UK clinical practice away from use of prosthetic grafts. The risk of Methicillin-resistant Staphylococcus aureus (MRSA) infection in prosthetic graft has been linked with a higher mortality rate than in patients undergoing autologous bypass. The GDG felt that random control trial (RCT) evidence does not accurately reflect these important issues.

Refer to the full version of the original guideline document for the specific "Trade off between clinical benefits and harms" for individual recommendations.

Contraindications

Contraindications

- Contrast-enhanced magnetic resonance angiography (CE MRA) is contraindicated in people with intra-cranial clips, pacemakers and in patients with renal insufficiency. In addition, some people are unable to tolerate magnetic resonance angiography (MRA) due to claustrophobia.
- Computed tomography angiography (CTA) is not recommended for people with an estimated glomerular filtration rate (eGFR) of <30ml/min. The latter is not an absolute contraindication but would also be considered a relative contraindication to CE MRA. If the creatinine is <200 CTA could be performed with safeguards.
- Naftidrofuryl oxalate is contraindicated in people with a history of hyperoxaluria or recurrent calcium-containing stones. The summary of product characteristics should be consulted for a full list of side effects and contraindications.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute of Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance. These are available on the NICE Web site ; see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Information Requirements

- Offer all people with peripheral arterial disease oral and written information about their condition. Discuss it with them so they can share decision-making, and understand the course of the disease and what they can do to help prevent disease progression. Information should include:
    - The causes of their symptoms and the severity of their disease
    - The risks of limb loss and/or cardiovascular events associated with peripheral arterial disease
    - The key modifiable risk factors, such as smoking, control of diabetes, hyperlipidaemia, diet, body weight, and exercise (see also recommendation on the secondary prevention of cardiovascular disease below)
    - How to manage pain
    - All relevant treatment options, including the risks and benefits of each
    - How they can access support for dealing with depression and anxiety

Ensure that information, tailored to the individual needs of the person, is available at diagnosis and subsequently as required, to allow people to make decisions throughout the course of their treatment.

Secondary Prevention of Cardiovascular Disease in People with Peripheral Arterial Disease

- Offer all people with peripheral arterial disease information, advice, support, and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance (see related NICE guidance; in section 6 of the original guideline document) on:
    - Smoking cessation
    - Diet, weight management and, exercise
    - Lipid modification and statin therapy
    - The prevention, diagnosis, and management of diabetes
    - The prevention, diagnosis, and management of high blood pressure
    - Antiplatelet therapy

Diagnosis

- Assess people for the presence of peripheral arterial disease if they:
    - Have symptoms suggestive of peripheral arterial disease or
    - Have diabetes, non-healing wounds on the legs or feet, or unexplained leg pain or
    - Are being considered for interventions to the leg or foot or
    - Need to use compression hosiery
- Assess people with suspected peripheral arterial disease by:
    - Asking about the presence and severity of possible symptoms of intermittent claudication and critical limb ischaemia
    - Examining the legs and feet for evidence of critical limb ischaemia, for example ulceration
    - Examining the femoral, popliteal, and foot pulses
    - Measuring the ankle brachial pressure index (see recommendation below)
- Measure the ankle brachial pressure index in the following way:
    - The person should be resting and supine if possible.
    - Record systolic blood pressure with an appropriately sized cuff in both arms and in the posterior tibial, dorsalis pedis and, where possible, peroneal arteries.
    - Take measurements manually using a Doppler probe of suitable frequency in preference to an automated system.
    - Document the nature of the Doppler ultrasound signals in the foot arteries.
    - Calculate the index in each leg by dividing the highest ankle pressure by the highest arm pressure.

Imaging for Revascularisation

- Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging (after duplex ultrasound) before considering revascularisation.

Management of Intermittent Claudication

- Offer a supervised exercise programme to all people with intermittent claudication.

Management of Critical Limb Ischaemia

- Ensure that all people with critical limb ischaemia are assessed by a vascular multidisciplinary team before treatment decisions are made.
- Do not offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Foreign Language Translations

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Lower limb peripheral arterial disease: diagnosis and management. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 28 p. (Clinical guideline; no. 147).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

National Guideline Centre - National Government Agency [Non-U.S.]

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National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

All members of the guideline development group (GDG) and all members of the National Clinical Guideline Centre (NCGC) staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required any actions. The details of declared interests are shown in Appendix B of the full version of the original guideline document.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Lower limb peripheral arterial disease. Diagnosis and management. Full guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 299 p. (Clinical guideline; no. 147). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Lower limb peripheral arterial disease: Diagnosis and management. Appendices. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 543 p. (Clinical guideline; no. 147). Electronic copies: Available in PDF from the NICE Web site .
- Lower limb peripheral arterial disease: Primary care. Clinical audit tools. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. (Clinical guideline; no. 147). Electronic copies: Available from the NICE Web site .
- Lower limb peripheral arterial disease. Costing report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 24 p. (Clinical guideline; no. 147). Electronic copies: Available in PDF from the NICE Web site .
- Lower limb peripheral arterial disease. Costing template. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 24 p. (Clinical guideline; no. 147). Electronic copies: Available from the NICE Web site .
- Lower limb peripheral arterial disease overview. NICE Pathways. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. (Clinical guideline; no. 147). Electronic copies: Available from the NICE Web site .
- The guidelines manual 2009. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Jan. Electronic copies: Available in Portable Document Format (PDF) from the NICE Archive Web site .

Patient Resources

The following is available:

- Lower limb peripheral arterial disease. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Aug. 18 p. (Clinical Guideline; no.149). Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on November 14, 2012. This summary was updated by ECRI Institute on October 28, 2013 following the U.S. Food and Drug Administration advisory on Acetaminophen. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines.

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